

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-460

ENVIRONMENTAL ASSESSMENT

**REVIEW OF
ENVIRONMENTAL ASSESSMENT**

**For
METAGLIP TABLETS
(Glipizide & Metformin HCl)**

NDA 21-460

**Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products
(HFD-510)**

Date Completed: October 18, 2002

EXECUTIVE SUMMARY - ENVIRONMENTAL ASSESSMENT**FONSI recommended.**

A FONSI was approved for metformin HCl (NDA 20-357) in Nov 1994 based on an EIC of 1.4 ppb and the review of the EA in Amendment # 32 dated Nov 8, 1994. NDA 21-460 refers to NDA 20-357 and contains an updated annual production estimate _____ for metformin HCl.

NDA 21-460 provides for a combination drug product containing metformin hydrochloride and glipizide. However, information in the EA in NDA 21-460 pertains to metformin hydrochloride only. Glipizide is categorically excluded from the requirement to prepare an Environmental Assessment because its EIC is ≤ 1 ppb.

Metformin hydrochloride is not volatile and will not enter the air compartment. Metformin hydrochloride is not expected to bind to sludge because its log octanol water partition coefficient is -1.25. Metformin hydrochloride is very soluble in water and therefore, it is expected to enter the aquatic environment through effluents discharged by publicly owned treatment works (POTW). The Expected Introduction Concentration (EIC_{aquatic}) is _____ assuming no metabolism, no hydrolysis and no direct photolysis. There is no absorption between 290 and 800 nm. The indirect photolysis half-life is 28 days. The Expected Environmental Concentration (EEC) in the aquatic environment is _____. The EEC was calculated using a dilution factor of 10 for wastewater effluents discharged into the receiving waters.

Environmental effect data were generated for aquatic species. It is unlikely that metformin hydrochloride represents a risk to the aquatic environment based on the available data.

Metformin hydrochloride Effects Testing Data

Microbial Inhibition (TAD 4.02)	Azotobacter	MIC 800 mg/mL
	Aspergillus niger	MIC > 1000 mg/mL
	Penicillium	MIC > 1000 mg/mL
	Chaetomium (fungi)	MIC > 1000 mg/mL
	Pseudomonas	MIC > 1000 mg/mL
	Anabaena (alga)	MIC 100 mg/mL
	Paramecium caudatum	MIC > 1000 mg/mL
Daphnia, acute (TAD 4.08)	48 hour EC ₅₀ = 130 mg/L	
	NOEC 78 mg/L	
Bluegill, acute (TAD 4.11)	NOEC 982 mg/L	

Summary: No significant environmental impact is anticipated based on the data submitted.

REVIEW of ENVIRONMENTAL ASSESSMENT

1. **Date:** EA dated Nov 12, 2001
Project Manager: James Cross
Chemist: Xavier Ysem
2. **Name of applicant/petitioner:** Bristol-Myers Squibb Company

ADEQUATE

3. **Address:** PO Box 4000, Princeton, NJ 08543-4000

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4. **Description of the proposed action:**

a. Requested Approval (NDA 21-460):

Bristol-Myers Squibb Company filed NDA 21-460 pursuant to section 505(b) of the Federal, Food, Drug & Cosmetic Act for Metaglip Tablets (metformin HCl and glipizide)

This submission requests approval of Metaglip Tablets for treatment of non-insulin dependent diabetes mellitus (NIDDM) in conjunction with control of diet and exercise.

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b. Need for Action:

- This submission requests approval of Metaglip Tablets for treatment of non-insulin dependent diabetes mellitus (NIDDM) in conjunction with control of diet and exercise.

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c. Expected Locations of Use (Drug Product):

Metaglip Tablets (metformin hydrochloride – glipizide) will be used in hospitals, clinics and patients' homes throughout the U.S.

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d. Disposal Sites

Empty or partially empty packages containing metformin hydrochloride and glipizide will be disposed by a community's solid waste management system, which may include landfills, incineration and recycling. Minimal quantities of unused drug may be disposed in the sewer system.

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5. Identification of the chemical that is the subject of the proposed action:

Metaglip is the trade name for the combination tablet containing metformin hydrochloride and glipizide. Information provided below pertains to metformin hydrochloride only because glipizide qualifies for categorical exclusion

- a. Nomenclature
 - i. Established Name (USAN): Metformin hydrochloride
 - ii. CAS Name: N,N-Dimethylimidodicarbonimidic diamide monohydrochloride.
- b. CAS Registration Number: Metformin hydrochloride salt, 1115-70-4
- c. [CAS Registration Number: Metformin, free base, 657-24-9]
- d. Molecular Formula, salt: _____
- e. Molecular Weight, salt: 165.63
- f. Chemical Structure is in Section 6.4 of the EA, page 0004

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6. Environmental Issues:

Glipizide is categorically excluded from the requirement to prepare an Environmental Assessment because its EIC is not more than 1 ppb.

Metformin hydrochloride is the active pharmacological ingredient in Glucophage Tablets, 500 mg and 850 mg (NDA 20-357). Metformin hydrochloride data and testing procedures performed according to GLPs and FDA EA-TAD were submitted on Nov 8, 1994 as Amendment # 32 to NDA 20-357. The FONSI for NDA 20-357 was approved on Nov 23, 1994.

The EA in NDA 21-460 includes a revised (increased) production estimate for metformin hydrochloride. It refers to NDA 20-357, Amendment # 32 for physiochemical, fate and effects data for metformin hydrochloride.

Environmental Fate of Released Substances

i. Identification of Substances of Interest

Metformin HCl is the active ingredient in Glucophage Tablets (NDA 20357) and Metaglip Tablets (NDA 21460). Summing all production estimates for all indications, the maximum annual production estimate is _____. This is equivalent to EIC = : _____ in the aquatic environment.

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ii. Physical and Chemical Characterization

Metformin hydrochloride exists as a cation in the environmental pH range. Solubility is reported to be ≈ 30 % wt/vol in water. (pH and temperature are not specified but these are insignificant qualifiers in this case.)

The log of the n-octanol / water partition coefficient ($\log P_{ow}$) is -1.25. Because $\log P_{ow}$ is not more than 3, the probability for bioaccumulation, adsorption to particulate matter, humic acids and sediments is low.

Vapor pressure of metformin hydrochloride is virtually nil. Therefore, vaporization into the atmosphere is not expected.

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iii. Environmental Depletion Mechanisms

Metformin hydrochloride is stable to direct photolysis, hydrolysis and aerobic biodegradation. The first order half-life for indirect photolysis (1% acetone sensitizer) is 28.3 days. Indirect photolysis provides an effective means for eliminating metformin hydrochloride from the environment.

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iv. Environmental Concentration, aquatic

The total amount of metformin hydrochloride required in the peak market is _____ (BMS provided this information in the CONFIDENTIAL part of the EA, Appendix 1, page 0011)

The Expected Introduction Concentration (EIC_{aquatic}) of metformin hydrochloride entering the external aquatic environment is _____. This assumes no metabolism. This is the concentration used in the risk assessment for effects on microorganisms and acute toxicity studies.

Adjusting EIC_{aquatic} by 10 fold dilution when metformin hydrochloride is introduced into the aquatic compartment gives the Expected Environmental Concentration, $EEC = \frac{EIC_{\text{aquatic}}}{10}$. To be conservative, EICs and EEC were not adjusted for removal by indirect photolysis.

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v. Summary

Metformin hydrochloride will enter the aquatic environment through effluents discharged by publicly owned treatment works (POTW). Metformin hydrochloride is not volatile and therefore will not enter the air compartment. Metformin hydrochloride is not expected to be persistent in the environment due to its potential for indirect photolysis.

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Environmental Effects of metformin hydrochloride

Environmental effect data for aquatic species are in Amendment # 32 submitted on Nov 8, 1994 to NDA 20-357. It is unlikely that metformin hydrochloride represents a risk to the aquatic environment based on the available data.

[Note that page 10 of the EA in NDA 21-460 is titled Metformin Effects where as the same table in NDA 20-357 is titled Metformin Hydrochloride Effects. The latter title corresponds to the text in the EA and therefore, it is likely to be correct. The title in the EA attached to the FONSI for NDA 21-460 was changed to correct the typographical error. Whether the reported results for effects correspond to the free base or the hydrochloride salt, a FONSI is still appropriate.]

Metformin Hydrochloride Effects Testing Data

Microbial Inhibition (TAD 4.02)	Azotobacter (N ₂ fix)	MIC 800 mg/mL
	Aspergillus niger (mold)	MIC > 1000 mg/mL
	Penicillium (mold)	MIC > 1000 mg/mL
	Chaetomium (fungi)	MIC > 1000 mg/mL
	Pseudomonas (soil bact)	MIC > 1000 mg/mL
	Anabaena (alga)	MIC 100 mg/mL
	Paramecium caudatum	MIC > 1000 mg/mL
Daphnia, acute (TAD 4.08)	48 hour EC ₅₀ = 130 mg/L	
	NOEC ≥ 78 mg/L	
Bluegill, acute (TAD 4.11)	NOEC ≥ 982 mg/L	

Summary of Metformin Hydrochloride Effects Data

The introduction of the metformin hydrochloride into sewage treatment plants and into the environment through use and disposal of the product is not expected to pose an environmental risk.

Based on the Microbial Inhibition Test (TAD 4.02), metformin hydrochloride does not inhibit the growth of microbial strains or species at concentrations expected in wastewater treatment plants. Therefore it is not expected to disrupt the ecosystem.

The applicant performed acute toxicity testing with daphnia magna and bluegill (*Lepomis macrochirus*).

Daphnia: The 48 hour EC₅₀ = 130 mg/L, the NOEC measured is more than 78 mg/L. The EC₅₀ to EIC ratio is greater than 1000. The NOEC is more than 1000 times greater than the EIC, namely —, indicating that no effects would be expected.

Bluegill: The NOEC measured is more than 982 mg/L. The NOEC is more than 1000 times greater than the EIC, namely —, indicating that no effects would be expected

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Summary Evaluation: Based on the above data, a FONSI is recommended

7. Mitigation Measures

No adverse environmental effects have been identified.
No mitigation measures are required.

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8. Alternatives to the proposed action

No potential effects have been identified for this proposed action.
No alternatives to the proposed action are required.

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9. Preparer

The name and professional experience of the EA preparer are provided

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10. References

Three references are provided.

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11. Appendices

The EA contains a data summary table in non-confidential Appendix 1.

The confidential Appendix 1 includes calculations of EIC (MEEC) and EEC based on the maximum annual production estimate in the next 5 years.

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Florian Zielinski, October 18, 2002

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/s/

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10/18/02 02:25:53 PM
ENV ASSESSMENT

Nancy Sager
10/18/02 02:36:28 PM
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10/18/02 04:22:36 PM
CHEMIST
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Bristol-Myers Squibb Company

glipizide and metformin HCl

Initial NDA

12.1 NONCONFIDENTIAL APPENDIX 1

The environmental fate and effect data are summarized in Table [IV.1.T01].

Table IV.1.T01: Metformin - Properties, Fate and Effects Data Summary

Physical/Chemical Characterization	
Water solubility	30.55 %
Partition coefficient (octanol/water) [Log Kow]	0.056 [-1.25]
Vapor Pressure	not measured; however, it is assumed to be quite low as the substance is a high melting solid;
Sorption Coefficient (K _{oc}), estimated	4.97
Depletion Mechanisms	
Hydrolysis	Does not hydrolyze at 50 degrees C for 5 days at pH values of 5, 7 or 9.
Aerobic Degradation	0.6% conversion to CO ₂ after 28 days.
Photolysis	Not conducted. No absorbance between 290 and 800 nm.
Indirect Photolysis	T _{1/2} estimated at 28.3 days
Environmental Effects	
Microbial Inhibition:	No inhibition @ 1000 ppm
Aspergillus, Penicillium, Chaetomium (fungi), Pseudomonas, Bacillus	
Anabaena (algae)	MIC = 100 ppm
Azobacter (Nitrogen fixing bacterium)	MIC = 800 ppm
Daphnia Magna Acute Toxicity (48 hr.)	{ NOEC = 78 mg/l; EC50 = 130 mg/l
Fish Acute Toxicity (Bluegills) (96 hr.)	
	NOEC = 982 mg/l

Table abbreviations: NOEC = No observed effects concentration; MIC = Minimum inhibitory concentration; EC50 = Concentration producing 50% immobilization

* Data reported for Metformin HCl
in NDA 20-357, Amendment #32, Nov 8, 94.
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